



## Newborn Screening Program

201 Townsend CV4  
PO Box 30195  
Lansing, MI 48909

P: (517) 335-4181 F: (517) 335-9419 / (517) 335-9739  
Website: [www.mi.gov/newbornscreening](http://www.mi.gov/newbornscreening)

## Interpretation of Newborn Hemoglobin Screening Results

There are more than 1,100 human hemoglobin variants. The majority were discovered during population surveys and are not associated with clinical manifestations.

The purpose of newborn hemoglobinopathy screening is to detect sickle cell disease. The most common types of sickle cell disease are sickle cell anemia (Hemoglobins SS), Hemoglobin SC disease, sickle beta thalassemia zero ( $S\beta^0$ ) and sickle beta thalassemia plus ( $S\beta^+$ ). These conditions render infants susceptible to overwhelming pneumococcal infection and acute splenic sequestration. These life-threatening complications may occur prior to other less severe complications that would lead to the routine diagnosis and institution of preventative measures. Infection and death can be virtually eliminated by continuous oral penicillin prophylaxis from age 3 months to 5 years. The recommended dose is 125mg BID until age 3 and 250mg BID until age 5.

Reference: Gaston et al NEJM June 1986

The methodology for initial newborn hemoglobin screening is high performance liquid chromatography (HPLC) and isoelectric focusing. A confirmatory test (hemoglobin electrophoresis) is required preferably before age 3 months. **A sickle cell screen (hemoglobin solubility or sickle dex) is not helpful in evaluating infants with possible sickle cell related conditions.**

In the newborn period a definitive diagnosis of hemoglobin SC disease can be made (the newborn test results would be FSC). However, only a presumptive diagnosis of sickle cell anemia (Hemoglobin SS disease) can be made. This is because the HPLC pattern typical of sickle cell anemia (FS) is also found in:

- Sickle cell beta thalassemia zero ( $S\beta^0$ ) which is clinically similar to sickle cell anemia.
- Sickle beta thalassemia plus ( $S\beta^+$ ) which is generally a mild form of sickle cell disease characterized by the presence of a small amount of adult hemoglobin. The HPLC pattern for  $S\beta^+$  is typically FSA but with a large amount of fetal hemoglobin may present as FS.
- Sickle cell with hereditary persistence of fetal hemoglobin (HPFH), which is a benign condition that does not require any intervention.

(See table 1 page 2)

**Table 1** Possible Outcomes with Initial Test Result of FS

DIAGNOSIS	CONFIRMATORY TEST **	CBC	FAMILY STUDIES
Sickle Cell Anemia (SS)	FS or SF	Low Hemoglobin Sickle cells on peripheral smear	Both parents AS
Sickle Beta Thalassemia Zero ( $S\beta^0$ )	FS or SF	Low Hemoglobin Low MCV Sickle cells on peripheral smear	One parent AS One parent AA with elevated HB A2
Sickle Beta Thalassemia Plus ( $S\beta^+$ )	FSA, SFA or SAF	Low MCV Mildly decreased or normal hemoglobin	Same as Sickle Beta Thal Zero
Sickle Cell with HPFH	FS or SF	Normal Hemoglobin Normal peripheral smear	One Parent AS One parent AF with Hb F approx. 20-30%

**\*\* Hemoglobins are generally reported in decreasing order of concentration**

NOTE: Family studies are extremely helpful in distinguishing between the above conditions but must be approached with caution because of the possibility of revealing non-paternity.

Newborn hemoglobinopathy screening will also identify:

1. Sickle cell trait and hemoglobin C and D trait – clinically benign but genetically significant carrier states associated with sickle cell disease.
2. Hemoglobin C disease and C thalassemia, mild forms of hemolytic anemia, which are of minor clinical significance and do not require early intervention.
3. Hemoglobin E trait, Hemoglobin E disease and E thalassemia (see Non-Sickle Reporting table).
4. Hemoglobin D disease and D thalassemia (see FC/FD Reporting Table)
5. Hemoglobin H disease
6. Some cases of Beta Thalassemia major (reported as low A).
7. The presence of other hemoglobin variants. Identification of the specific variant in the newborn period is not possible with the current methodology.

**Newborn hemoglobinopathy screening will not identify beta thalassemia trait.**

**Note:** If an increased amount of adult hemoglobin for birth weight is noted, the infant is presumed to have been transfused. A repeat newborn screening specimen is needed at least three months after the last transfusion when the transfused blood should no longer be present if there is no valid hemoglobin result in the infant's record.

### **Comment on hemoglobin variants reported as "V"**

The methodology used by the MDCH, NBS Laboratory specifically detects hemoglobins A, S, C, D, E, F and a FAST region that includes Bart's hemoglobin. If hemoglobins other than those specified are detected, they are reported as "V". These unidentified hemoglobins invariably have no or minimal clinical or genetic significance and could create unnecessary parental anxiety. Therefore we do not report FAV results to parents, only to the physician of record on the newborn screening card.

### **Comment on Bart's Hemoglobin**

Bart's hemoglobin is detected by newborn screening when there is a deletion of one or more of the four alpha globin genes. If a newborn screening report includes "Bart's ", the NBS specimen is forwarded to the Children's Hospital of Oakland Research Institute (CHORI) molecular diagnostics laboratory for further testing. The purpose of this further testing is to identify all three gene deletions (Hemoglobin H disease), however some two gene deletions will also be identified:

- Two alpha genes deletions (alpha thalassemia trait) permits nearly normal erythropoiesis but there is a mild microcytic anemia. The disease in this form can be mistaken for iron deficiency anemia and treated inappropriately with iron. With both the cis and trans form of the mutation the family may be at risk for having a child with Hb H disease in the future. With the cis form the family may also be at risk for having a child with hydrops fetalis.
- Three alpha gene deletions (Hemoglobin H Disease) can result in moderate to severe anemia, sometimes requiring transfusions.

In the Reporting Tables that follow:

**SCDAA is the Sickle Cell Disease Association of America, Michigan Chapter.**

The Michigan Department of Community Health designated medical management center.

P: 313-864-4406 (toll-free 800-842-0973). Fax: 313-864-9980.

Contact Person: Wanda Whitten-Shurney MD

**Note:** The SCDAA and MDCH provide information to the physician listed on the newborn screening card. Unfortunately this is often not the physician who is actually caring for the child. Efforts are made to locate the infant's primary care provider but are sometimes unsuccessful.



Note: Hemoglobins are generally reported in decreasing order of concentration.

**FS REPORTING TABLE**

The following table includes the most commonly reported FS hemoglobin results.

RESULT CODE	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
<b>FS</b> Fetal and sickle hemoglobin	<ul style="list-style-type: none"><li>• Sickle cell anemia</li><li>• Sickle cell-β thalassemia zero or plus</li><li>• Sickle cell – hereditary persistence of fetal hemoglobin, a benign condition</li></ul>	Action required is dependent on the results of the confirmatory test.  <u>Disease Conditions:</u> <ul style="list-style-type: none"><li>▪ Penicillin prophylaxis</li><li>▪ Disease Education</li><li>▪ Referral to Pediatric Hematology/Oncology</li></ul>
<b>FSA</b> Fetal hemoglobin, sickle hemoglobin and small amount of adult hemoglobin	<ul style="list-style-type: none"><li>• Sickle β-thalassemia plus</li><li>• Sickle cell trait</li></ul>	
<b>FSC</b> Fetal hemoglobin, sickle hemoglobin and hemoglobin C	<ul style="list-style-type: none"><li>• Hemoglobin SC disease; generally a milder form of sickle cell disease sometimes confused with sickle cell trait</li></ul>	<u>Sickle Cell Trait and phenotypically similar conditions:</u> <ul style="list-style-type: none"><li>▪ Reassurance</li><li>▪ Genetic Counseling</li><li>▪ Offer family testing</li></ul>
<b>FSD</b> Fetal hemoglobin, sickle hemoglobin and hemoglobin D	<ul style="list-style-type: none"><li>• Hemoglobin SD disease – moderate sickling disorder</li></ul>	
<b>FSV</b> Fetal hemoglobin, sickle hemoglobin and an unidentified variant	<ul style="list-style-type: none"><li>• Sickle cell anemia</li><li>• Sickle cell-β thalassemia</li><li>• Sickle cell – hereditary persistence of fetal hemoglobin (benign)</li><li>• Hemoglobin S C Harlem - moderate sickling disorder</li><li>• Hemoglobin S O Arab – moderate sickling disorder</li><li>• Conditions phenotypically identical to sickle cell trait</li></ul>	
<b>FSE</b> Fetal hemoglobin, sickle hemoglobin and hemoglobin E	<ul style="list-style-type: none"><li>• Hemoglobin SE Disease</li><li>• A mild form of sickle cell disease similar to sickle beta thalassemia plus</li></ul>	

The Patient Advocates from the SCDA will attempt to contact the family, inform the parents of the diagnosis, assist in obtaining the required confirmatory test, provide standardized disease education, assist in initiating penicillin prophylaxis when indicated and refer to pediatric hematology/oncology if appropriate. Our patient advocates also monitor penicillin compliance quarterly and provide nonmedical (social work) services to clients of all ages.

## **FC / FD REPORTING TABLE**

The following table includes the most commonly reported FC and FD hemoglobin results.

RESULT CODE	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
<b>FC</b> Fetal hemoglobin and hemoglobin C	<ul style="list-style-type: none"><li>• Hemoglobin C disease; usually a mild form of hemolytic anemia with no need for intervention in the newborn period</li><li>• Hemoglobin C thalassemia zero or plus</li></ul>	For all cases: <ul style="list-style-type: none"><li>• Confirmatory Testing</li><li>• Genetic Counseling</li><li>• Education about Condition (brochure)</li><li>• Offer family testing</li></ul>
<b>FCE</b> Fetal hemoglobin, hemoglobin C and hemoglobin E	<ul style="list-style-type: none"><li>• Hemoglobin CE disease; a benign, but genetically significant, condition</li></ul>	
<b>FCA</b> Fetal hemoglobin, hemoglobin C and small amount of adult hemoglobin	<ul style="list-style-type: none"><li>• Hemoglobin C thalassemia plus; usually a mild form of hemolytic anemia with no need for intervention in the newborn period</li><li>• Hemoglobin C trait</li></ul>	
<b>FCV</b> Fetal hemoglobin, hemoglobin C and unidentified hemoglobin variant	<ul style="list-style-type: none"><li>• Hemoglobin C Disease</li><li>• Hemoglobin C Thalassemia</li><li>• Conditions phenotypically identical to hemoglobin C trait</li></ul>	
<b>FDA</b> Fetal hemoglobin, hemoglobin D and small amount of adult hemoglobin	<ul style="list-style-type: none"><li>• Hemoglobin D thalassemia; a benign condition</li><li>• Hemoglobin D trait</li></ul>	
<b>FDV</b> Fetal hemoglobin, hemoglobin D and unidentified hemoglobin variant	<ul style="list-style-type: none"><li>• Hemoglobin D Disease; a benign condition</li><li>• Hemoglobin D thalassemia</li><li>• Conditions phenotypically identical to hemoglobin D trait</li></ul>	
<b>FD</b> Fetal hemoglobin and hemoglobin D	<ul style="list-style-type: none"><li>• Homozygous hemoglobin D; a benign condition</li><li>• Hemoglobin D thalassemia</li></ul>	

The SCDAA has the responsibility of informing the parents of the diagnosis, assisting in obtaining the required confirmatory test, providing written information about the condition and making appropriate referrals.

## **FE / Low A REPORTING TABLE**

The following table includes the most commonly reported non-sickle hemoglobin results.

RESULT CODE	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
<b>Low A</b>	<ul style="list-style-type: none"><li>Possible beta thalassemia major</li></ul>	<ul style="list-style-type: none"><li>Confirmatory testing</li><li>Referral to Heme/Onc if appropriate</li></ul>
<b>FE</b> Fetal hemoglobin and hemoglobin E	<ul style="list-style-type: none"><li>Hemoglobin E disease; a mild form of hemolytic anemia.</li><li>Hemoglobin E thalassemia; a more severe form of hemolytic anemia causing transfusion dependence</li></ul>	<ul style="list-style-type: none"><li>Confirmatory testing</li><li>Genetic counseling</li><li>Referral to Heme/Onc if appropriate</li></ul>
<b>FEA</b> Fetal hemoglobin, hemoglobin E and a small amount of adult hemoglobin	<ul style="list-style-type: none"><li>Hemoglobin E thalassemia; a more severe form of hemolytic anemia causing transfusion dependence</li><li>Hemoglobin E trait</li></ul>	<ul style="list-style-type: none"><li>Confirmatory testing</li><li>Genetic counseling</li><li>Referral to Heme/Onc if appropriate</li></ul>
<b>FEV</b> Fetal hemoglobin, hemoglobin E and unidentified hemoglobin variant	<ul style="list-style-type: none"><li>Hemoglobin E disease</li><li>Hemoglobin E thalassemia</li><li>Conditions phenotypically identical to hemoglobin E trait</li></ul>	<ul style="list-style-type: none"><li>Confirmatory testing</li><li>Genetic counseling</li><li>Referral to Heme/Onc if appropriate</li></ul>
<b>FV</b> Fetal hemoglobin and unidentified hemoglobin variant	<ul style="list-style-type: none"><li>Unknown variant hemoglobin disease</li></ul>	<ul style="list-style-type: none"><li><b>MDCH will send specimen to reference lab for further analysis.</b></li><li><b>SCDAA will provide information to parents and physician of record</b></li></ul>

The SCDAA has the responsibility of informing the parents of the diagnosis, assisting in obtaining the required confirmatory test, providing written information about the condition with a follow-up phone call to answer questions, and making appropriate referrals.

## **S,C,D,E TRAIT REPORTING TABLE**

The following table includes the most commonly reported trait hemoglobin results.

RESULT	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
<b>FAS</b> Fetal hemoglobin, normal adult and sickle hemoglobin	<ul style="list-style-type: none"> <li>Sickle cell trait; which is clinically benign but genetically significant</li> </ul>	<ul style="list-style-type: none"> <li>No confirmatory testing required.</li> <li>Genetic counseling</li> </ul>
<b>FAC</b> Fetal hemoglobin, normal adult and hemoglobin C	<ul style="list-style-type: none"> <li>Hemoglobin C trait; which is clinically benign but genetically significant</li> </ul>	<ul style="list-style-type: none"> <li>No confirmatory testing required.</li> <li>Genetic counseling</li> </ul>
<b>FAD</b> Fetal hemoglobin, normal adult and hemoglobin D	<ul style="list-style-type: none"> <li>Hemoglobin D trait; which is clinically benign but genetically significant</li> </ul>	<ul style="list-style-type: none"> <li>No confirmatory testing required.</li> <li>Genetic counseling</li> </ul>
<b>FAE</b> Fetal hemoglobin, normal adult and hemoglobin E	<ul style="list-style-type: none"> <li>Hemoglobin E trait; which is clinically benign but genetically significant</li> </ul>	<ul style="list-style-type: none"> <li>No confirmatory testing required.</li> <li>Genetic counseling</li> </ul>

The SCDA will send a letter to the mother with the diagnosis and an explanation of its significance including a brochure about the various sickle cell conditions. A follow-up phone call will be made by the patient advocate to verify that letter was received, answer questions, and offer a face to face educational session and family testing if desired.

## **FAV/FABart's Reporting Table**

The following table includes the FAV and FABart's reporting.

RESULT	DIAGNOSTIC POSSIBILITIES	ACTION REQUIRED
<b>FAV</b> Fetal hemoglobin, normal adult and an unidentified hemoglobin variant	<ul style="list-style-type: none"> <li>Most likely clinically insignificant hemoglobin variant</li> </ul>	<ul style="list-style-type: none"> <li>Physician of record responsible for reassuring the parent that this is clinically insignificant.</li> <li>No confirmatory testing required.</li> </ul>
<b>FABart's</b> Fetal Hemoglobin, Hemoglobin A and Bart's Hemoglobin	<ul style="list-style-type: none"> <li>Hemoglobin H disease</li> <li>Alpha Thalassemia Trait</li> </ul>	<ul style="list-style-type: none"> <li>MDCH will send specimen to reference lab for further analysis.</li> <li>SCDA will provide information to parents and physician of record for clinically significant findings.</li> </ul>